Effect of liraglutide 3.0 mg on glycaemic control in individuals with overweight/obesity and type 2 diabetes treated with basal insulin: results from the SCALE Insulin trial

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Introduction

- Liraglutide 3.0 mg is approved for weight management in individuals with overweight or obesity and has been investigated in individuals with type 2 diabetes (T2D) as part of the Satiety and Clinical Adiposity—Liraglutide Evidence (SCALE) phase 3a program.[1]
- In SCALE Diabetes, a 56-week trial in individuals with overweight or obesity and T2D, liraglutide 1.8 mg and 3.0 mg showed significant weight- and glucose-lowering effects, with an acceptable safety profile.[2] However, individuals treated with insulin were excluded from the trial.
- To our knowledge, no pharmacotherapeutic agents approved for the treatment of obesity have been specifically investigated in individuals with obesity and insulin-treated T2D.
- The aim of the SCALE Insulin phase 3b trial was to evaluate the efficacy and safety of liraglutide 3.0 mg for weight management in individuals with overweight or obesity and T2D treated with basal insulin and up to two oral antidiabetic drugs (OADs). This poster reports the measures of glycaemic control and hypoglycaemic safety data from the trial.

Methods

Study design

- SCALE Insulin (NCT02963922) was a 56-week, randomised, double-blind, placebo-controlled, multicentre trial in individuals with obesity.
- A total of 396 adults with T2D (HbA_{1c} 6.0–10.0%) and overweight or obesity (body mass index [BMI] ≥27 kg/m^2) were randomised 1:1 to liraglutide 3.0 mg or placebo, both as adjunct to intensive behaviour therapy (IBT).
- An IBT program was provided in both arms which included reduced caloric intake, increased physical activity goals (increasing up to 250 min/week) and 23 behavioural counselling sessions.
- The diabetes treatment regimens for all individuals included basal insulin and up to two OADs. It was recommended that doses of sulphonylureas were reduced by 50% at randomisation to avoid the risk of hypoglycaemia.
  - » Individuals on sulphonylureas were stratified between two arms.
- Similarly, doses of basal insulin were recommended to be reduced by 15–20% for individuals who had HbA_{1c} ≤8%. The trial was designed such that glycaemic control was similar between the two arms (e.g. insulin doses adjusted weekly).
- Weekly dose escalation of the trial drug was implemented during the first 4 weeks at randomisation in accordance with the label.[2]

Statistical analysis

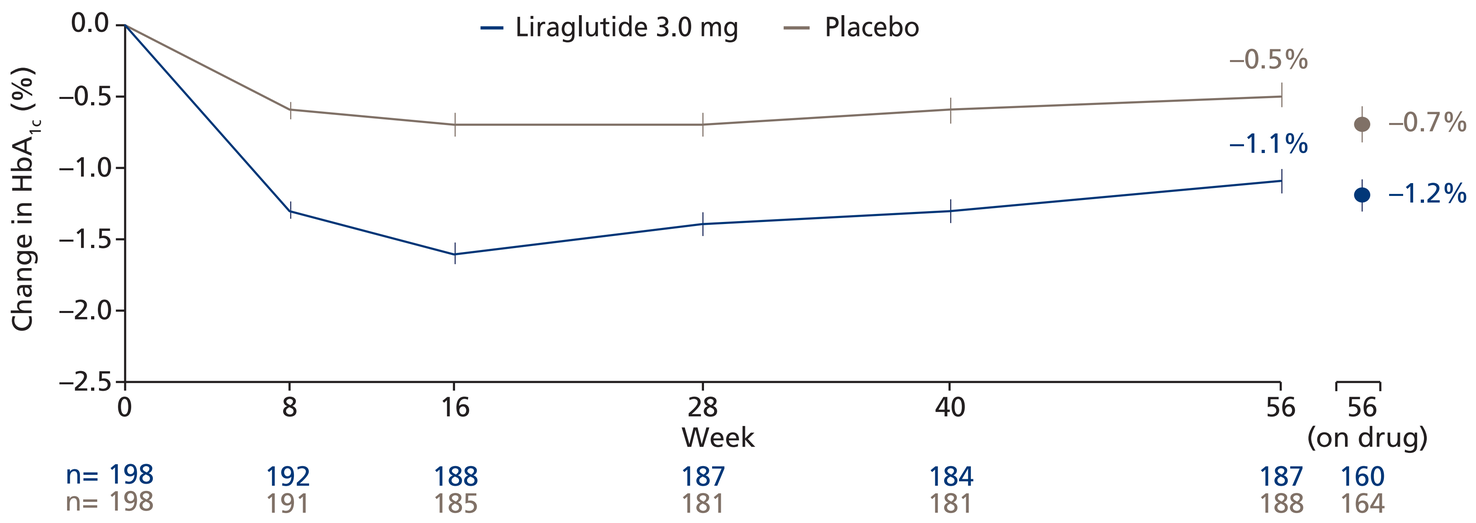
- Outcomes were assessed based on data for all randomised individuals regardless of premature discontinuation of trial product (treatment policy estimand or intention-to-treat [ITT] principle); missing values were handled using a jump-to-reference multiple imputation model.
- Continuous and categorical variables were calculated using analysis of covariance (ANCOVA) and logistic regression respectively, with treatment arm, gender and BMI as factors and baseline endpoint as a covariate.

Results

- In total 396 individuals were randomised (1:1) to liraglutide 3.0 mg or placebo, of which 195 and 197 were exposed, respectively.
- To increase retention, the trial allowed individuals to return to study drug after discontinuation. At 56 weeks, 166 (83.8%) and 168 (84.8%) individuals remained on liraglutide 3.0 mg and placebo, respectively.
- Baseline demographics were similar between treatment arms (Table 1).

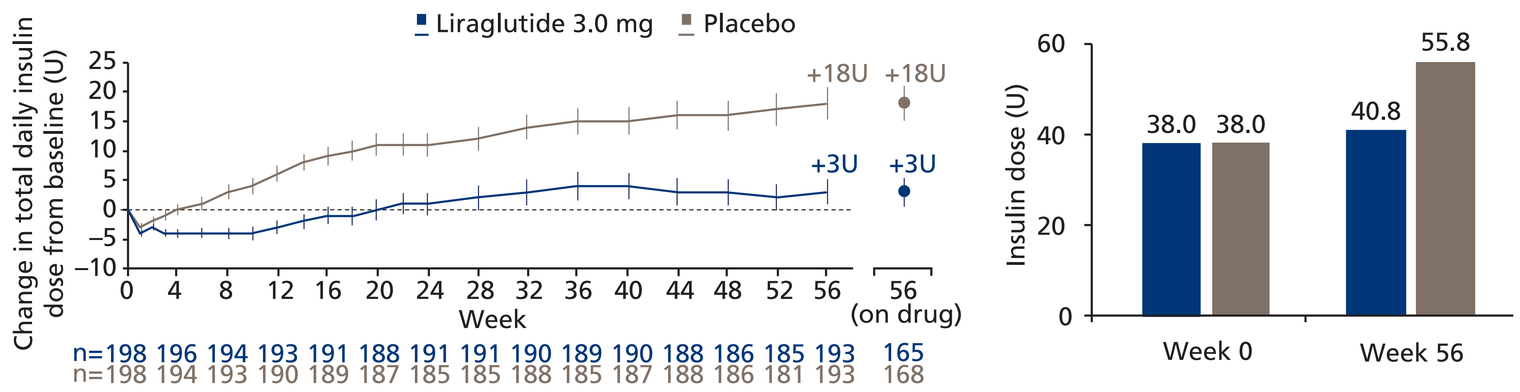
Figure 1: Change in HbA_{1c} over time (%)

Key result



Graph is observed mean data ± standard error of the mean.

Figure 2: Change in total daily insulin dose (U)



Over-time graph is observed mean data ± standard error of the mean. The bar plot is based on observed baseline data and estimated mean at week 56.

Table 1: Baseline demographics and anthropometry

	Liraglutide 3.0 mg (n=198)	Placebo (n=198)
Sex, male, n (%)	90 (45.5)	99 (50.0)
Mean age, years (SD)	55.9 (11.3)	57.6 (10.4)
Race, white, n (%)	174 (87.9)	180 (90.9)
Mean body weight, kg	100.6 (20.8)	98.9 (19.9)
Mean BMI, kg/m^2 (SD)	35.9 (6.5)	35.3 (5.8)
Mean HbA_{1c}, % (SD)	7.9 (1.1)	8.0 (1.0)
Mean FPG, mmol/L (SD)	7.8 (2.2)	8.1 (2.5)
Mean diabetes duration, years	11.4 (6.8)	12.8 (6.9)
Anti-diabetic medications at screening		
SGLT2-is, n (%)	44 (22.2)	44 (22.2)
Sulphonylureas, n (%)	68 (34.3)	71 (35.9)
Long-acting basal insulins/ analogues, n (%)	180 (90.9)	184 (92.9)
Intermediate-acting basal insulins/analogues, n (%)	18 (9.1)	14 (7.1)

Values are observed mean (SD) for full analysis set, unless otherwise stated. BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation; SGLT2-i; sodium-glucose co-transporter-2 inhibitor.

- Mean estimated change in weight at 56 weeks was –5.85% and –1.53% with liraglutide 3.0 mg and placebo, respectively, corresponding to an estimated treatment difference (ETD) of –4.32% (95% confidence interval [CI]: –5.48; –3.16, p<0.0001).
- Mean estimated change in HbA_{1c} at 56 weeks was –1.09% and –0.55% with liraglutide 3.0 mg and placebo, respectively (ETD: –0.53, 95% CI: –0.76; –0.31, p<0.0001) (Figure 1).
- Mean estimated change in fasting plasma glucose at 56 weeks was –1.02 and –0.64 mmol/L (ETD: –0.39, 95% CI: –0.91; 0.14, p=not significant).
- At 56 weeks, more liraglutide 3.0 mg than placebo-treated individuals achieved the composite endpoint of reaching HbA_{1c} target[3] <7.0% + ≥5% weight loss (39.0% vs. 13.9%; odds ratio 3.94, p<0.0001). Similarly, more liraglutide 3.0 mg than placebo-treated individuals met the composite endpoint of HbA_{1c} <7.0% + ≥5% weight loss + no documented symptomatic hypoglycaemia[4] (17.8% vs. 6.2%; odds ratio 3.28, p=0.0006).
- Mean insulin dose increased by +2.8U and +17.8U (ETD –15U, p<0.0001) with liraglutide and placebo, respectively, from a baseline mean (both groups) of 38U (Figure 2).
- Total number of hypoglycaemic events (on-drug) occurred at respective rates of 742 and 938 events per 100 patient-years of exposure with liraglutide and placebo, with three and two severe events, respectively (Table 2).

Table 2: Hypoglycaemic episodes* from randomisation to week 56

	Liraglutide 3.0 mg				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of individuals	195				197			
Hypoglycaemic episodes	140	(71.8)	1462	742.3	140	(71.1)	1859	937.9
Severe episodes	3	(1.5)	3	1.5	2	(1.0)	2	1.0
BG ≤3.9 mmol/L								
Asymptomatic	116	(59.5)	742	376.7	116	(58.9)	988	498.4
Documented symptomatic	92	(47.2)	662	336.1	102	(51.8)	816	411.7

Data are from patients on-drug. Episodes recorded in patient diaries. BG, blood glucose; E, number of events; R, event rate per 100 patient-years of exposure. *Based on American Diabetes Association 2013 criteria[4]

Conclusion

- In insulin-treated individuals with longstanding T2D and overweight/obesity, adding liraglutide 3.0 mg resulted in better glycaemic control versus placebo in addition to clinically relevant weight loss, with need for less basal insulin.
- More hypoglycaemic episodes were reported in individuals treated with placebo than liraglutide 3.0 mg.

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References: (**1**) Novo Nordisk. Saxenda® EU SmPC. Available at: https://www.ema.europa.eu/; (**2**) Davies *et al. JAMA* 2015;314:687–99; (**3**) American Diabetes Association. *Diabetes Care* 2019;42(Suppl 1):S61–S70; (**4**) Seaquist *et al. Diabetes Care* 2013;36:1384–95.